November 30, 2000

Reo Menning
Deputy Director
Silicones Environmental, Health and Safety Council
11921 Freedom Drive Suite 550
Reston, VA 20190

Dear Ms. Menning:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 3-(2,3-epoxypropoxy)propyltrimethoxysilane (TMSPGE; CAS # 2530-83-8), submitted July 20, 2000. I commend the Silicones Environmental, Health and Safety Council for their commitment to the HPV Challenge Program and encourage you to take appropriate steps to make your submission a successful contribution.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

As explained in the enclosed comments, SEHSC needs to articulate support for its conclusion that a screening level characterization of TMSPGE is feasible without reproductive toxicity data. The arguments SEHSC outlines in its proposal need to be strengthened by providing better documentation and incorporation of a discussion of structure-activity relationships for the reproductive effects of siloxanes.

In the event that a reproductive test is necessary, I would like to point out that this submission is for an individual chemical, and as stated in the October 14, 1999 letter to sponsors (http://www.epa.gov/chemrtk/ceoltr2.htm), animal testing for SIDS endpoints for individual chemicals shall be deferred until November, 2001.

SEHSC also needs to supply better support for its conclusion that the submitted ecological data are adequate. The ecotoxicity robust summaries contain insufficient information to permit an assessment of data adequacy. SEHSC needs to supply more information about the existing studies, if available, and reevaluate testing needs in light of their adequacy.

As with other submissions where the available data are either inadequate or insufficiently documented, this case will remain open until adequate documentation is in hand.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that SEHSC advise the Agency, within 60 days of the posting on the Chemical RTK website, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-260-3470. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@.epa.gov.

I thank you for your submissions and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
C. Auer
N. Patel
A. Abramson

EPA Comments on Chemical RTK HPV Challenge Submission:

3-(2,3-Epoxypropoxy)propyltrimethoxysilane

SUMMARY OF EPA COMMENTS

The sponsor, the Silicones Environmental, Health and Safety Council (SEHSC), submitted a Test Plan and Robust Summaries to EPA dated July 20, 2000 for 3-(2,3-Epoxypropoxy)propyltrimethoxysilane (TMSPGE; CAS # 2530-83-8). EPA posted the submission on the ChemRTK Web site on August 3, 2000.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical and Environmental Fate Data. The sponsor's approach to these endpoints is generally acceptable. The proposed hydrolysis studies will provide important information that will aid in the interpretation of the health effects, environmental effects and transport/distribution endpoints. Although EPA agrees with the sponsor's conclusion that transport/distribution estimates are not meaningful for the parent compound because of the expected rapid hydrolysis, such calculations may be appropriate for the trisilanol hydrolysis product.

2. It is important to note that alkoxysilanes present special challenges owing to their ready reactivity with water. This affects the measurement and interpretation of their environmental fate and their toxicity. EPA suggests that in such situations, sponsors who identify the known or probable structures of decomposition and degradation products can help EPA and other reviewers to better evaluate and interpret the available data.

3. Health Endpoint: Reproductive Toxicity. The sponsor proposes not to conduct a reproductive toxicity study for a variety of reasons. To support this conclusion, the sponsor needs to supply the information identified below under "Test Plan."

4. Other Health Endpoints: Three of the six submitted robust summaries lack information needed to allow for an independent assessment of the data. The sponsor needs to submit adequate documentation as discussed below in "Specific Comments on Robust Summaries" so reviewers can judge whether data are adequate.

5. Ecotoxicity. The summaries contain insufficient information to permit an independent assessment of data, in part because of special chemical properties that create a need for more details. The expected rapid hydrolysis of this chemical complicates interpretation of the available ecological toxicity data. The sponsor needs to submit the information discussed below in "Specific Comments on Robust Summaries" so reviewers can judge whether data are adequate.

EPA is requesting that the Sponsor advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE 3-(2,3-EPOXYPROPOXY)PROPYLTRIMETHOXYSILANE CHALLENGE SUBMISSION

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

The boiling point and vapor pressure results given for TMSPGE are acceptable, as is the sponsor's determination that the remaining chemistry endpoints are inappropriate for this water-sensitive chemical. However, it appears that measured boiling point data may be available (see under "Specific Comments on Robust Summaries"), and as a rule the measured value is preferred.

Fate (photodegradation, stability in water, biodegradation, and transport/distribution).

The sponsor's approach to the fate endpoints for TMSPGE is generally acceptable.

The Test Plan shows a table of hydrolysis half-lives ranging from 3 seconds to 4 hours depending on pH. The sponsor did not submit robust summaries for this endpoint and plans to confirm the data by additional hydrolysis studies (Table 2 in the Test Plan indicates that hydrolysis data are adequate; this is inconsistent with the planned testing and the lack of a robust summary).

If the sponsor plans to follow OECD Test Guideline 111 for hydrolysis studies, EPA suggests the following amendments/modifications to the protocol: (1) because TMSPGE is reported to be hydrolytically unstable, the procedure described on pp. 7-8 of the protocol should be followed. EPA suggests that the sponsor also perform the optional hydrolysis test at pH 1.2 as described on p. 8 of the protocol (to assess hydrolysis in the context of health effects tests); (2) because of the reported potential for polymerization and cross-linking of hydrolysis products in water (see below under comment on the biodegradation robust summaries), EPA suggests that the sponsor analyze the hydrolysis products to determine the extent to which polymerization and crosslinking occur.

Although EPA agrees with the sponsor's conclusion that transport/distribution estimates are not meaningful for the parent compound because of the expected rapid hydrolysis, such calculations may be appropriate for the trisilanol hydrolysis product unless there is information showing that this product is unstable even at high dilution. In order to estimate environmental fate endpoints EPA recommends using the EQC level III model from the Canadian Environmental Modeling Centre at Trent University. This model can be found at the following Web address: http://www.trentu.ca/academic/aminss/envmodel/.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

According to the sponsor, and confirmed by a search of EPA's TSCATS database, there are no reproductive toxicity data for this chemical. The sponsor proposes not to conduct a reproductive study on the basis that there is (1) polymerization of the test article in the stomach following oral exposure; (2) a necrotizing effect of the test article following dermal exposure; and (3) a lack of exposure via inhalation due to a very low saturated vapor concentration (12 ppm). The sponsor did not provide sufficient data to support these arguments.

First, the report referenced to show that the test article polymerizes in the stomach of rats (WIL-401001) does not support the statements presented on page 7 of the Test Plan because (a) there was no hypothesis/protocol described to show the purpose of the study; (b) no controls were discussed in the report; and (c) the test article listed as "present" in the stomach and/or intestine was not confirmed by analysis. Second, there were no data presented supporting the statement about dermal necrosis. Third, two inhalation studies have been conducted on this test material (both with aerosol concentrations greater than 12 ppm) according to industry reports in EPA's files (8EHQ-1191-1462).

More importantly, the sponsor focused on why a test cannot be performed because of potential problems handling or administering the chemical, but failed to articulate support for its conclusion that a screening level characterization of TMSPGE is feasible without reproductive toxicity data.

Therefore, to support the proposal not to perform a reproductive toxicity test, the sponsor needs to submit the following: a) characterization of hydrolysis/polymerization products in the hydrolysis test; b) a discussion of the available data with respect to the potential for bioavailability and toxicity (e.g., a study in EPA files (8EHQ-1191-1462) showed some developmental toxicity at a dose of 3000 mg/kg/day in rats, which is a high dose but nonetheless shows that test material was bioavailable); and c) a more thorough analysis of the structure-activity relationship of TMSPGE and siloxanes with reproductive toxicity (some organosiloxanes have been shown to cause reproductive effects in male (Tox. Appl. Pharm., [1972], Vol. 21, pp. 55-67) and female (Tox. Appl. Pharm., [1972], Vol. 21, pp. 68-79) animals (organosiloxanes are among the expected hydrolysis/polymerization products of TMSPGE)), including the possible role of the epoxide in TMSPGE, the reproductive effects observed with other siloxanes, and whether SIDS-level type tests would detect such effects.

Ecological Effects.

The ecotoxicity robust summaries contain insufficient information to permit an assessment of data adequacy, in part because of special chemical properties that create a need for more details. Rapid hydrolysis of this chemical is expected and complicates interpretation of the available ecological toxicity

data. In order to support the conclusion that existing data are adequate, the sponsor needs to supply more information about existing studies, if available, including test substance preparation and administration. Where available data cannot satisfy the data needs, the measured water hydrolysis test planned by the sponsor will help to determine the appropriate test method for the parent substance, hydrolysis product, or both. EPA therefore will use the forthcoming hydrolysis data in its evaluation of the adequacy of the data and test plan for ecological effects.

SPECIFIC COMMENTS ON ROBUST SUMMARIES

Chemistry

The physicochemical data reported in the robust summaries were: vapor pressure, 0.3 Pa @ 20°C (0.0023 torr @ 20°C)(calculated from vapor pressures measured at elevated temperatures); boiling point, 262°C @ 101.3 kPa (760 torr) (calculated from the vapor pressure data).

EPA identified some published physicochemical data for this chemical in the literature for comparison with the data in the Robust Summaries:

> A boiling point of 260 - 262°C at 760 torr (Fluka Catalog) agreed well with the submitted value; EPA calculated from this a vapor pressure of 0.012 torr using NOMO5–a program that estimates boiling point and vapor pressure from measured values grouped by chemical class.
>
> From a boiling point of 120°C at 2.0 torr (Aldrich Catalog) EPA estimated a value of 284°C at 760 torr and a vapor pressure of 0.0028 torr @ 25°C (NOMO5).
>
> EPA performed an EPI estimate for this chemical for comparison purposes: boiling point: 253°C (Adapted Stein & Brown method); vapor pressure: 0.0142 torr @ 25°C.

The data shown in the robust summaries reviewed generally agree with the published data in the literature and the estimated data.

Fate

Biodegradation

The submitter classified this chemical as "not readily biodegradable." The biodegradability of the substance was determined using a DOC Die-Away Test. EPA notes that the test results are more precisely a measure of the biodegradability of the hydrolysis products than of the parent chemical. In practical terms these processes can't be separated and the results are due to both processes.

The rapid loss of DOC between days 0 and 7 followed by little additional biodegradation on days 14-28 is consistent with the rapid hydrolysis of the parent compound followed by rapid biodegradation of the methanol hydrolysis products, as postulated by the sponsor. The glycidyoxylalkyl trisilanol hydrolysis product may not be degraded under the conditions of the test. If it were, DOC loss would have increased more significantly after day 7.

These results are adequate for assessing the ready biodegradability of the parent compound. However, there is a potential concern for the silanol hydrolysis product, which can be assumed from the test data to be not readily biodegradable. EPA questions the submitter's unqualified statement that the silanol hydrolysis product forms cross-linked products in water (more information about this reaction might have been helpful). At some point the solution of silanol products may become too dilute for the molecules to react rapidly with one another. Yet, in principle, these silanols could still exert ecotoxicity.

Health Effects

EPA evaluated six health endpoint robust summaries and found three of them to be inadequate for the purposes of the U.S. HPV Challenge Program. In all cases, the missing information was detailed incidence data by dose for apparent effects observed. The sponsor needs to submit the information so EPA and other reviewers can conduct an independent assessment of the studies and evaluate the test plan.

The two acute toxicity and *in vitro* genetic toxicity summaries were considered adequate for the purposes

of the Challenge Program.

The following EPA comments reflect the information in the robust summary (the full study report may address these comments):

Genetic Toxicity (Ames Test): Although the robust summary is acceptable for the Challenge Program, the following information would enhance the summary: (a) the rationale for the dose selection; (b) whether cytotoxicity was observed (and at what doses); and (c) the criteria for a positive response. EPA notes with interest the multiple *in vitro* studies performed in mammalian cells that are reported as supporting information and that appear to have both positive and negative results.

Genetic Toxicity (*In vivo* Micronucleus Study): This robust summary is considered inadequate because the incidence of micronucleated polychromatic erythrocytes by dose group is not provided.

Repeat Dose Toxicity: This robust summary is considered inadequate because it did not identify the effects - and incidence by dose for those effects - showing "statistical differences from control values."

Developmental Toxicity Study: This robust summary is considered inadequate because it did not provide the incidence by dose for the external, visceral or skeletal alterations observed.

Finally, EPA would like to commend the sponsor for providing substantial supporting information for many of the health endpoints in an abbreviated summary format. EPA found this information useful in its review.

Ecotoxicity Studies

EPA agrees with the submitter that this chemical is difficult to test in aquatic systems. Proper testing of such chemicals may follow the Revised Draft Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD, January 2000 - available on the OECD website at http://www.oecd.org/ehs/test/monos.htm). This formal guidance was not available at the time the data in question were generated. Among the most important considerations is the stability of the test substance; recommended test conditions depend on the hydrolysis half-life value. Information related specifically to the testing of alkoxysilanes also appears under "Alkoxysilanes" in the document "TSCA New Chemicals Program (NCP): Chemical Categories", available at www.epa.gov/oppt/newchems/chemcat.htm. While the latter guidance was developed for a different purpose, it contains useful technical information.

Thus, in order to evaluate the adequacy of the ecotoxicity data for silanes, it is essential to have reliable stability in water (hydrolysis) data. Determination of this endpoint is part of the sponsor's test plan.

In addition, especially given this chemical's reactivity with water, the sponsor needs to furnish any further details relevant to this factor in the studies. For example, it is important to know whether undiluted test substance was added directly to the exposure vessels or whether the sample was prepared in water before initiation of the test, with the sample solution existing long enough for significant sample hydrolysis to occur before exposure of the animals. In the former case, the actual substance tested could be mostly starting material, while in the latter the tested material could be mostly hydrolysis products. Additional details about sample preparation, storage and administration are needed to allow reviewers to better judge the data adequacy and interpret the results.

The comments below reflect the information presented in the robust summaries; information in the full study report may address some of the issues identified. EPA used its robust summary guidance document (http://www.epa.gov/opptintr/chemrtk/guidocs.htm) as a guide in reviewing these data.

Acute Aquatic Toxicity. Robust summaries were submitted for studies on fish, daphnia, and green algae (one study summary for each organism). The summaries could not be adequately evaluated because of the following deficiencies in reporting:

Robust summary-fish. Information on the preparation and administration techniques are not detailed enough to determine if the chemical was introduced in a dropwise manner while stirring or how long the test solution aged before exposing the organisms. These two factors are crucial in determining the ecological hazard and determining whether any toxicity is due to the parent or hydrolysis product. Definitive (replicate) tests were not done to confirm the nominal LC50 values observed in the tests. Exposure concentrations were not analytically verified. The supporting fish acute data also lacked key information including TOC, analytical measurement, and information on test substance preparation and dosing techniques.

Robust summary–aquatic plant. The robust summary did not include information on pH, background TOC, hardness, and test conditions such as number of replicates, stock solution preparation and dosing method to help determine if the data are adequate.

Robust summary-daphnid. Critical information on dosing and preparation of the test substance has not been submitted to help determine data adequacy. Data elements missing from the robust summary include background TOC, dissolved oxygen, and analytical verification of test concentrations. The test species used (*Simocephalus vetulus*) is not a preferred species for the aquatic invertebrate test; the sponsor needs to supply documentation to support its use compared to well-characterized recommended test species such as *Daphnia magna*. It is unclear from the data whether the duration of the test was 48 or 96 hours, because both exposure times were mentioned in the submitted robust summary.

Followup Activity

EPA requests that the Sponsor advise the Agency within 60 days of any modifications to its submission.